Availability of Comparative Efficacy Data at the Time of Drug Approval in the United States

Nikolas H. Goldberg
Sebastian Schneeweiss, MD, ScD
Mary K. Kowal, BA
Joshua J. Gagne, PharmD, MS

IN 2009, CONGRESS ALLOCATED $1.1 billion to comparative effectiveness research through the American Recovery and Reinvestment Act. According to the Institute of Medicine, such research is defined as the “generation and synthesis of evidence that compares the benefits and harms of alternative methods to prevent, diagnose, treat, and monitor a clinical condition or to improve the delivery of care.”

A key objective of comparative effectiveness research is to inform evidence-based treatment decisions made by patients and prescribers. Comparative effectiveness information is also crucial for formulary and coverage decisions. Large-scale, randomized, head-to-head comparisons of multiple treatments are generally regarded as the gold standard for comparing the efficacy of medical interventions but are costly and time consuming. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), which compared the incidence of cardiovascular events and death among patients treated with 1 of 4 antihypertensive medications, with or without lipid-lowering therapy, cost $100 million and took 8 years to complete.

Observational studies of comparative effectiveness are increasingly conducted, because they allow for simultaneous comparisons of multiple medical products, represent care in routine practice, and can be completed at a fraction of the cost of most clinical trials. In most situations, observational studies also may be more quickly completed than randomized trials.

However, comparative effectiveness information on drugs is most useful to decision-makers shortly after marketing authorization. Publicly available FDA approval packages contain comparative efficacy data for about half of NMEs recently approved in the United States and for more than two-thirds of NMEs for which alternative treatment options exist. We did not investigate the extent to which available comparative efficacy information is useful for clinical guidance.
marketing approval, when observational
data from routine care and data from
large head-to-head trials comparing
multiple treatments are not yet avail-
able. This raises the question about
the extent to which preapproval data
could inform comparative effective-
ness decisions in the early marketing
phase. Although reliance on placebo-
controlled studies without active con-
trol groups generates much debate,9
little systematic evidence is available
regarding the accessibility of compara-
tive efficacy data when drugs are
approved. Such data were available for
roughly half of the drugs approved in
Europe between 1999 and 2005.7 How-
ever, the European Medicines Agency
recommends the use of both active and
placebo comparators when possible,8
whereas the US Food and Drug Admin-
istration (FDA) does not.9
We sought to determine the propor-
tion of recently approved drugs that had
comparative efficacy data available at
the time of market authorization in the
United States and to examine trends in
availability of this information over time
and by therapeutic indication.

METHODOLOGY

Data Source and Extraction
We obtained data from the publicly ac-
cessible Drugs@FDA database.10 We
identified all new molecular entities
(NMEs) approved from 2000 through
2010, excluding diagnostic agents, hy-
aluronidase, and sunscreens. We in-
cluded therapeutic biologic products
contained in the database, such as
monoclonal antibodies, cytokines,
growth factors, enzymes, immuno-
modulators, and thrombolytics, but the
database does not include all biologics
approved during the study period.
For each eligible NME, we accessed
the drug approval packages and deter-
mined whether any of the efficacy stu-
dies that supported the approved indi-
cation used active comparators. The
approval packages often contain mul-
tiple documents, including approval
letters, medical reviews, chemistry
reviews, pharmacology reviews, and sta-
tistical reviews. We considered an NME
to have active comparator data if at least
1 efficacy study, described in any of
these documents, included an active
comparator. We required that the effi-
cacy study be one that supported the
approved indication; that is, the eli-
gible trials were generally phase 3, un-
less only phase 2 studies were the ba-
sis for approval (as with darunavir), and
the eligible trials studied end points rel-
vant to the approved indication(s). The
active comparator must have been ap-
proved by the FDA by the time the NME
was approved. In some cases data were
only available from ongoing clinical
studies, which we included if the inter-
im results were reported. We did not
include studies that used historical
controls. Furthermore, we required that
efficacy results of the comparison be-
tween the NME and the active com-
parator be reported in the approval
documents.
We determined whether the NME of
interest (drug A) was compared with a
specific alternative treatment option
(eg, drug A vs drug B) or standard care
alone (eg, drug A + standard care vs
placebo + standard care). We also ex-
ttracted information on the approval
date, whether the drug was an orphan
product, the review classification (ie,
priority or standard), the approved in-
dication(s), and whether the approval
decision was based primarily on pla-
cebo-controlled or active drug–
controlled trial data. Two investiga-
tors (N.H.G., M.K.K.) independently
extracted data and made each determi-
nation. Discrepancies were discussed
and resolved by consensus.

Analysis
We calculated the proportion (and 95%
confidence interval [CI]) of approved
NMEs with available comparative effi-
cacy data and cross-tabulated the pro-
portion by therapeutic indication and
year of authorization. We inspected the
variation in proportions over time by
plotting them by year of authoriza-
tion. We then fit a multivariable logis-
tic regression model to adjust for tem-
poral effects that could be attributable
to trends in priority review approvals
and trends in types of drugs approved,
with respect to therapeutic indication.
We conducted this analysis at the in-
dividual NME level, with availability of
comparative efficacy data as the depen-
dent variable and with indicators of year
of market authorization as our main ex-
planatory variables of interest.
We further included indicators of re-
view status and therapeutic indication
to adjust for temporal changes in pri-
ority review designations and types of
drugs approved. We transformed esti-
imated log odds for each year from the
logistic regression model to probabili-
ties and plotted them. We performed
all statistical analyses in SAS version 9.2
(SAS Institute Inc, Cary, North Caro-
lina).

RESULTS
We identified 197 eligible approved
NMEs between 2000 and 2010, of
which a high of 24 were approved in
2000 and 2004 and a low of 14 were
approved in 2005 and 2007 (TABLE).
One hundred NMEs (51% [95% CI,
44%-58%]) had comparative efficacy
data available at the time of market
authorization. FDA approval was
based primarily on active-control data
for 59 NMEs, which was 59% (95% CI,
49%-68%) of NMEs approved
with any comparative efficacy data
available and 30% (95% CI, 24%-37%)
of all NMEs approved during
the study period.
After excluding orphan products
(n=37) and other NMEs approved for
indications for which no alternative
treatments existed (n=17), the propor-
tion with available comparative effi-
cacy data increased to 70% (95% CI,
62%-77%). On a yearly basis, the propor-
tion of NMEs with comparative effi-
cacy data (excluding orphan drugs
and those for which no alternative treat-
ment existed) varied between 50% (95%
CI, 21%-79%) in 2008 and 92% (95%
CI, 65%-100%) in 2010.
Availability of comparative efficacy
data was more common for some
therapeutic indications, including dia-
abetes mellitus (89% [95% CI, 56%-99%])
and infectious diseases (73%
[95% Cl, 54%–87%]), than others, such as hormones and contraceptives (33% [95% Cl, 9%–67%]), cancer (35% [95% Cl, 18%–54%]), and genitourinary tract conditions (38% [95% Cl, 16%–66%]). After excluding orphan drugs and products approved for indications for which no alternative treatments existed, the proportions by therapeutic indications were more similar. After adjusting for therapeutic indication and priority review status in the multivariable model, the estimated trend in proportion of NMEs with comparative efficacy data over time was not meaningfully different from the unadjusted trend. Compared with those drugs that received standard review designations, NMEs that received priority review designations were much less likely to have comparative efficacy data (odds ratio, 0.24 [95% Cl, 0.11–0.53]).

**COMMENT**

Overall, about half of all new drugs approved in the United States since 2000 were compared with an alternative treatment prior to market authorization, and the results of this comparison were publicly available in the FDA approval packages. For NMEs approved for indications with existing alternative treatment options, the proportion of approvals with comparative efficacy data increased to roughly two-thirds. Drugs with priority review designations were less likely to have comparative efficacy data available. Whether active comparators are used in clinical trials likely depends not only on the availability of a reasonable alternative or established standard of care but also on the ethics of placebo controls for the given indications. For example, when an alternative treatment existed, most NMEs approved for cancer and human immunodeficiency virus/AIDS had comparative efficacy information available.

Although comparative efficacy data meeting our minimal criteria were available for approximately half of all newly approved NMEs, we did not assess the extent to which the publicly available data are informative enough to provide a basis for prescribing and coverage decisions. The FDA and the Centers for Medicare & Medicaid Services recently issued a memorandum of understanding stating that the organizations will work together to promote initiatives related to the review and use of FDA-regulated products. While the memorandum lacks details, one stated goal of the partnership is to establish processes that meet common needs for evaluating, among other things, the efficacy and coverage of medications. A step in that direction would be to further increase the proportion of NMEs with preapproval comparative efficacy studies and to improve the accessibility of such information at the time of FDA approval. Another avenue for broader accessibility and dissemination would be independent drug information providers, such as http://www.RxFacts.org. Making the data more accessible to clinicians and payers can help maximize their utility in prescribing and coverage decisions. To our knowledge, approval information is not widely used for making decisions in the postapproval setting.

Our definition of what constituted availability of comparative efficacy data was quite liberal. We required a minimum of 1 study with a single active comparator, although prescribers and payers often must make decisions among multiple alternatives, even within a single class. Further, the proportion of drugs with available comparative efficacy information may be slightly overestimated by our exclusion of therapeutic biologic products not available in the Drugs@FDA database.

---

**Table. Proportion of New Molecular Entities With Comparative Efficacy Data Available in Their Approval Packages by Year of Authorization and Therapeutic Indication**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All NMEs</th>
<th>All NMEs Excluding Orphan and First-in-Class Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>100/197 (51)</td>
<td>100/143 (70)</td>
</tr>
<tr>
<td>Year of authorization</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2000</td>
<td>13/24 (54)</td>
<td>13/20 (65)</td>
</tr>
<tr>
<td>2001</td>
<td>11/21 (52)</td>
<td>11/18 (61)</td>
</tr>
<tr>
<td>2002</td>
<td>9/16 (56)</td>
<td>9/10 (90)</td>
</tr>
<tr>
<td>2003</td>
<td>12/21 (57)</td>
<td>12/16 (78)</td>
</tr>
<tr>
<td>2004</td>
<td>10/24 (42)</td>
<td>10/14 (71)</td>
</tr>
<tr>
<td>2005</td>
<td>6/14 (43)</td>
<td>6/8 (75)</td>
</tr>
<tr>
<td>2006</td>
<td>7/16 (44)</td>
<td>7/12 (58)</td>
</tr>
<tr>
<td>2007</td>
<td>8/14 (57)</td>
<td>8/10 (80)</td>
</tr>
<tr>
<td>2008</td>
<td>5/16 (31)</td>
<td>5/10 (63)</td>
</tr>
<tr>
<td>2009</td>
<td>8/16 (50)</td>
<td>8/13 (62)</td>
</tr>
<tr>
<td>2010</td>
<td>11/15 (73)</td>
<td>11/12 (62)</td>
</tr>
<tr>
<td>Therapeutic indication</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>8/9 (89)</td>
<td>8/9 (89)</td>
</tr>
<tr>
<td>Infectious diseases</td>
<td>19/26 (73)</td>
<td>19/25 (76)</td>
</tr>
<tr>
<td>HIV/AIDS</td>
<td>7/11 (64)</td>
<td>7/9 (78)</td>
</tr>
<tr>
<td>Psychiatric conditions</td>
<td>10/16 (63)</td>
<td>10/14 (71)</td>
</tr>
<tr>
<td>Cardiovascular and cerebrovascular conditions</td>
<td>15/25 (60)</td>
<td>15/20 (75)</td>
</tr>
<tr>
<td>Arthritis and rheumatism</td>
<td>3/5 (60)</td>
<td>3/4 (75)</td>
</tr>
<tr>
<td>Neurologic conditions</td>
<td>9/18 (50)</td>
<td>9/15 (60)</td>
</tr>
<tr>
<td>Gastrointestinal tract conditions</td>
<td>4/9 (44)</td>
<td>4/5 (80)</td>
</tr>
<tr>
<td>Ocular conditions</td>
<td>4/10 (40)</td>
<td>4/7 (57)</td>
</tr>
<tr>
<td>Genitourinary tract conditions</td>
<td>5/13 (38)</td>
<td>5/10 (50)</td>
</tr>
<tr>
<td>Cancer</td>
<td>9/26 (35)</td>
<td>9/11 (62)</td>
</tr>
<tr>
<td>Hormones and contraceptives</td>
<td>3/9 (33)</td>
<td>3/5 (60)</td>
</tr>
<tr>
<td>Other</td>
<td>4/20 (20)</td>
<td>4/9 (44)</td>
</tr>
</tbody>
</table>

Abbreviations: HIV, human immunodeficiency virus; NME, new molecular entity.
base, because we expect that only a small proportion of approved biotechnological products would have head-to-head data available in approval packages. Nevertheless, our results, based on US approvals from 2000 through 2010, are in line with those of a similar study based on European approvals between 1999 and 2005. Many of the approved products overlap in the 2 studies, and US and European approvals are likely based on the same pre-marketing trials.

In conclusion, we found that publicly available documents include results of at least 1 head-to-head trial with an approved alternative for approximately half of all newly approved NMEs. Strategies are needed to enhance the accessibility of, and ultimately the use of, this information, particularly in the early marketing experience, when comparative effectiveness data from other sources are scarce or nonexistent.

**Author Contributions:** Dr Gagne had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Goldberg, Schneeweiss, Gagne. Acquisition of data: Goldberg, Kowal, Gagne. Analysis and interpretation of data: Goldberg, Schneeweiss, Kowal, Gagne. Drafting of the manuscript: Goldberg, Gagne. Critical revision of the manuscript for important intellectual content: Schneeweiss, Kowal, Gagne. Statistical analysis: Goldberg, Gagne. Obtained funding: Schneeweiss.

**REFERENCES**